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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Rodney Rothstein et al.
Serial No.: 09/814,661 Examiner: K. Canella
Filed: March 22, 2001 Art Unit: 1642
For: SMALL PROTEIN THAT INTERACTS WITH A RIBONUCLEOTIDE
REDUCTASE SUBUNIT AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
March 8, 2005

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the PTO-1449 form attached hereto as **Exhibit A**. Copies of references 3, 4, 7, 8 and 46-66 are attached hereto as **Exhibits 1-25**, respectively.

1. U.S. Patent No. 4,889,806 issued December 26, 1989 to Olson et al.;
2. U.S. Patent No. 5,834,279 issued November 10, 1998 to Rubin et al.;
3. U.S. Application No. 09/159,858, filed September 24, 1998, on behalf of Rodney Rothstein et al. (**Exhibit 1**);
4. PCT International Application No. PCT/US99/22260, filed

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September 24, 1999, International Publication No. WO 00/17225 A3, published March 30, 2000, on behalf of The Trustees of Columbia University In The City Of New York **(Exhibit 2)**;

5. European Patent Application No. EP 0 726 277 A2, published August 14, 1996, on behalf of Toshiaki et al.;
6. International Search Report issued on May 3, 2000 in connection with PCT International Application No. PCT/US99/22260, filed September 24, 1999, International Publication No. WO 00/17225 A3, published March 30, 2000, on behalf of The Trustees of Columbia University In The City Of New York;
7. Written Opinion issued on September 12, 2000 in connection with PCT International Application No. PCT/US99/22260, filed September 24, 1999, International Publication No. WO 00/17225 A3, published March 30, 2000, on behalf of The Trustees of Columbia University In The City Of New York **(Exhibit 3)**;
8. International Preliminary Examination Report issued on January 11, 2001 in connection with PCT International Application No. PCT/US99/22260, filed September 24, 1999, International Publication No. WO 00/17225 A3, published March 30, 2000, on behalf of The Trustees of Columbia University In The City Of New York **(Exhibit 4)**;
9. Arap, W. et al. (1998) "Cancer Treatment by Targeted Drug

Delivery to Tumor Vasculature in a Mouse Model," *Science* 279: 377-380;

10. Allen, J.B. et al. (1994) "The SAD1/RAD53 protein kinase controls multiple checkpoints and DNA damage-induced transcription in yeast," *Genes Dev.* 8: 2401-2415;
11. Barlow, C. et al. (1996) "Atm-Deficient Mice: A Paradigm Of Ataxia Telangiectasia," *Cell* 86: 159-171;
12. Desany, B.A. et al. (1998) "Recovery from DNA replicational stress Is the essential function of the S-phase checkpoint pathway," *Genes Dev.* 12: 2956-70;
13. Elledge, S.J. (1996) "Cell cycle checkpoints: preventing an identity crisis," *Science* 274: 1664-1672;
14. Elson, A. et al. (1996) "Pleiotropic defects in ataxia-telangiectasia protein-deficient mice," *Proc. Natl. Acad. Sci. USA* 93: 13084-13089;
15. Fay, D.S. et al. (1997) "Mutations in *SPK1/RAD53* that specifically abolish checkpoint but not growth-related functions," *Curr. Genet.* 31: 97-105;
16. James, P. et al. (1996) "Genomic libraries and a host strain designed for highly efficient two-hybrid selection in yeast," *Genetics* 144: 1425-1436;
17. Kato, R. et al. (1994) "An essential gene, *ESR1*, is

required for mitotic cell growth, DNA repair and meiotic recombination in *Saccharomyces cerevisiae*," *Nucleic Acids Res.* 22: 3104-3112;

18. Koch, C. et al. (1993) "A role for the transcription factors Mbp1 and Swi4 in progression from G1 to S phase," *Science* 261: 1551-1557;
19. Lecrenier, N. et al. (1995) "Overexpression of the *RNR1* gene rescues *Saccharomyces cerevisiae* mutants in the mitochondrial DNA polymerase-encoding *MIP1* gene," *Mol. Gen. Genet.* 249: 1-7;
20. Liuzzi, M. et al. (1994) "A potent peptidomimetic inhibitor of HSV ribonucleotide reductase with antiviral activity *in vivo*," *Nature* 372: 695-698;
21. Reichard, P. (1988) "Interactions between deoxyribonucleotide and DNA synthesis," *Ann. Rev. Biochem.* 57: 349-374;
22. Sanchez, Y. et al. (1996) "Regulation of *RAD53* by the *ATM*-like kinases *MEC1* and *TEL1* in yeast cell cycle checkpoint pathways," *Science* 271: 357-360;
23. Shewach, D.S. et al. (1996) "Gemcitabine and radiosensitization in human tumor cells," *Invest. New Drugs* 14: 257-263;
24. Shiloh, Y. (1997) "Ataxia-telangiectasia and the Nijmegen

breakage syndrome: related disorders but genes apart,"
Annu. Rev. Genet. 31: 635-662;

25. Sun, Z. et al. (1996) "Spkl/Rad53 is regulated by Mec1-dependent protein phosphorylation in DNA replication and damage checkpoint pathways," *Genes Dev.* 10: 395-406;
26. Szekeres, T. et al. (1994) "Biochemical and antitumor activity of trimidox, a new inhibitor of ribonucleotide reductase," *Cancer Chemther. Pharmacol.* 34: 63-66;
27. Vallen, E.A. et al. (1999) "Interaction between the *MEC1*-dependent DNA synthesis checkpoint and G1 cyclin function in *Saccharomyces cerevisiae*," *Genetics* 151: 459-71;
28. Wang, Y.A. et al. (1997) "Loss of *p21* increases sensitivity to ionizing radiation and delays the onset of lymphoma in *atm*-deficient mice," *Proc. Natl. Acad. Sci. USA* 94: 14590-14595;
29. Westphal, C.H. et al. (1997) "Genetic interactions between *atm* and *p53* influence cellular proliferation and irradiation-induced cell cycle checkpoints," *Cancer Res.* 57: 1664-1667;
30. Xu, Y. et al. (1996) "Targeted disruption of *ATM* leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma," *Genes Dev.* 10: 2411-2422;

31. Xu, Y. et al. (1996) "Dual roles of ATM in the cellular response to radiation and in cell growth control," *Genes Dev.* 10: 2401-2410;
32. Zakian, V.A. (1995) "ATM-related genes: what do they tell us about functions of the human gene?," *Cell* 82: 685-687;
33. Zheng, P. et al. (1993) "SPK1 is an essential S-phase-specific gene of *Saccharomyces cerevisiae* that encodes a nuclear serine/threonine/tyrosine kinase," *Mol. Cell. Biol.* 13: 5829-5842;
34. Barrell et al. (1997) (Genbank Accession No. Z46729, National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland);
35. Lewin (1988) "When Does Homology Mean Something Else?" *Science* 237: 1570;
36. Miyakawa et al. (1991) Genbank Accession No. X54964 (National Center for Biotechnology Information, National Library of Medicine; Bethesda, Maryland);
37. Reeck et al. (1987) "Homology In Proteins and Nucleic Acids: A Terminology Muddle and a Way Out of It," *Cell* 50: 667;
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39. Devlin et al. (1997) Genbank Accession No. Q04964, Hypothetical 11.8 kD protein in OGG1-CNA2 intergenic region, Gene Sequence;
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41. Cawthon et al. (1991) "cDNA Sequence and Genomic Structure of EVI2B, a Gene Lying Within An Intro of the Neurofibromatosis Type 1 Gene," *Genomics* 9: 446-460;
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45. Saitoh et al. (1991) *Biomed. Res.* 12: 215-218;
46. Bradford, M.M. (1976) "A Rapid and Sensitive Method For The Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding," *Anal. Biochem.* 72: 248-254 (**Exhibit 5**);
47. Chance, B. and Herbert, D. (1950) "The Enzyme-substrate Compounds of Bacterial Catalase and Peroxides," *J.*

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Biochem. 46: 402-414 (**Exhibit 6**);

48. Davis, R. et al. (1994) "Purification, Characterization and Localization of Subunit Interaction Area of Recombinant Mouse Ribonucleotide Reductase R1 Subunit," *J. Biol. Chem.* 269: 23171-23176 (**Exhibit 7**);
49. Elledge, S.J. and Davis, R.W. (1987) "Identification And Isolation of the Gene Encoding the Small Subunit of Ribonucleotide Reductase from *Saccharomyces cerevisiae*: DNA Damage-Inducible Gene Required for Mitotic Viability," *Mol. Cell. Biol.* 7: 2783-2793 (**Exhibit 8**);
50. Elledge, S.J. and Davis, R.W. (1990) "Two Genes Differentially Regulated in the Cell Cycle and By DNA-damaging Agents Encode Alternative Regulatory Subunits Of Ribonucleotide Reductase," *Genes Dev.* 4: 740-751 (**Exhibit 9**);
51. Engström, Y. et al. (1979) "Ribonucleotide Reductase from Calf Thymus. Purification and Properties," *Biochemistry* 18: 2941-2948 (**Exhibit 10**);
52. Huang, M. and Elledge, S.J. (1997) "Identification of *RNR4*, Encoding a Second Essential Small Subunit of Ribonucleotide Reductase in *Saccharomyces cerevisiae*," *Mol. Cell. Biol.* 17: 6105-6113 (**Exhibit 11**);
53. Hurd, H.K. et al. (1987) "Identification of the Gene for the Yeast Ribonucleotide Reductase Small Subunit and Its

Inducibility by Methyl Methanesulfonate," *Mol. Cell. Biol.* 7: 3673-3677 (**Exhibit 12**);

54. Ingemarson, R. and Thelander, L. (1996) "A Kinetic Study on the Influence of Nucleoside Triphosphate Effectors on Subunit Interaction in Mouse Ribonucleotide Reductase," *Biochemistry* 35: 8603-8609 (**Exhibit 13**);
55. Jönsson, U. et al. (1991) "Real-Time Biospecific Interaction Analysis Using Surface Plasmon Resonance and a Sensor Chip Technology," *BioTechniques* 11: 620-627 (**Exhibit 14**);
56. Lycksell, P.-O. et al. (1994) "¹H NMR Studies of Mouse Ribonucleotide Reductase: The R2 Protein Carboxyl-Terminal Tail, Essential for Subunit Interaction, Is Highly Flexible But Becomes Rigid in the Presence of Protein R1," *Biochemistry* 33: 2838-2842 (**Exhibit 15**);
57. Mann, G.J. et al. (1991) "Purification and Characterization of Recombinant Mouse and Herpes Simplex Virus Ribonucleotide Reductase R2 Subunit," *Biochemistry* 30: 1939-1947 (**Exhibit 16**);
58. Reichard, P. (1988) "Interactions Between Deoxyribonucleotide And DNA Synthesis," *Annu. Rev. Biochem.* 57, 349-374 (**Exhibit 17**);
59. Reichard, P. (1993) "From RNA to DNA, Why So Many Ribonucleotide Reductases?" *Science* 260: 1773-1777

(Exhibit 18);

60. Rova, U. et al. (1995) "Evidence by Site-Directed Mutagenesis Supports Long-Range Electron Transfer in Mouse Ribonucleotide Reductase," *Biochemistry* 34: 4267-4275 (Exhibit 19);
61. Studier, F.W. et al. (1990) "Use of T7 RNA Polymerase to Direct Expression of Cloned Genes," *Methods Enzymol.* 185: 60-89 (Exhibit 20);
62. Thelander, L. et al. (1980) "Ribonucleotide Reductase from the Calf Thymus: Separation of the Enzyme into Two Nonidentical Subunits, Proteins M1 and M2," *J. Biol. Chem.* 255: 7426-7432 (Exhibit 21);
63. Thelander, L. and Gräslund, A. (1994) "Ribonucleotide Reductase in Mammalian Systems," *Metal Ions In Biological Systems* (Marcel Dekker; New York): 109-129 (Exhibit 22);
64. Wang, P.J. et al. (1997) "Rnr4p, a Novel Ribonucleotide Reductase Small-Subunit Protein," *Mol. Cell. Biol.* 17: 6114-6121 (Exhibit 23);
65. Weinert, T. (1998) "DNA Damage and Checkpoint Pathways: Molecular Anatomy and Interactions with Repair," *Cell* 94: 555-558 (Exhibit 24); and
66. Zhao, X. et al. (1998) "A Suppressor of Two Essential

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Checkpoint Genes Identifies a Novel Protein that
Negatively Affects dNTP Pools," Mol. Cell 2: 329-340
(Exhibit 25).

The subject application is a §371 national stage application and claims the benefit under 35 U.S.C. §120 of PCT International Application No. PCT/US99/22260, filed September 24, 1999, which claims the benefit under 35 U.S.C. §120 of U.S. Application No. 09/159,858, filed September 24, 1998, which is now abandoned. Copies of these applications are attached hereto as **Exhibits 1 and 2**, respectively.

A Written Opinion was issued on September 12, 2000 in connection with PCT International Application No. PCT/US99/22260, filed September 24, 1999. A copy of the Written Opinion is attached hereto as **Exhibit 3**.

An International Preliminary Examination Report was issued on January 11, 2001 in connection with PCT International Application No. PCT/US99/22260, filed September 24, 1999. A copy of the International Preliminary Examination Report is attached hereto as **Exhibit 4**.

Above listed references 9-33 were submitted to and considered by the United States Patent and Trademark Office in an Information Disclosure Statement filed on August 27, 1999 in connection with U.S. Serial No. 09/159,858, filed September 24, 1998. Above listed references 6 and 39 were submitted to and considered by the United States Patent and Trademark Office in a Supplemental Information Disclosure Statement

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filed on October 6, 2000 in connection with U.S. Serial No. 09/159,858, filed September 24, 1998. Also, above listed references 1 and 34-38 were cited by the United States Patent and Trademark Office in an Office Action dated April 6, 2000 in connection with U.S. Serial No. 09/159,858, filed September 24, 1998. Furthermore, above listed references 2, 5 and 40-45 were cited by the United States Patent and Trademark Office in an Office Action dated December 18, 2000 in connection with U.S. Serial No. 09/159,858, filed September 24, 1998. Accordingly, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office since they were previously submitted to or cited by the United States Patent and Trademark Office in an application relied upon for an earlier filing date under 35 U.S.C. §120.

Pursuant to 37 C.F.R. §1.97(c)(2), the required fee for filing this Information Disclosure Statement is ONE HUNDRED AND EIGHTY DOLLARS (\$180.00) and a check for this amount is enclosed.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed \$180.00 fee, is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount

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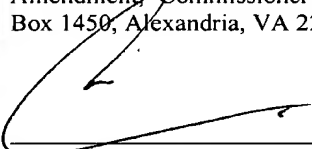
of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



Alan J. Morrison
Reg. No. 37,399

3/8/01
Date

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

[illegible]

Examiner Initials*	Cite No. ¹	Foreign Patent Document Country Code ³ Number ⁴ Kind Code ⁵ (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T ⁶
	4	WO 00/17225 A3	03-30-2000	The Trustees of Columbia University in the City of New York	
	5	EP 0726 277 A2	08-14-1996	Toshiaki et al.	

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***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹Applicant's unique citation designation number (optional). ² See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English Language Translation is attached.

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Exhibit A

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Application Number	09/814,661
	Filing Date	March 22, 2001
	First Named Inventor	Rodney Rothstein
	Art Unit	1642
	Examiner Name	K. Canella
	Attorney Docket No.	0575/56615-A-PCT-US/JPW/AJM/MVM

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	3	U.S. Application No. 09/159,858, filed September 24, 1998, on behalf of Rodney Rothstein et al.;	
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	13	ELLEDGE, S.J. (1996) "Cell cycle checkpoints: preventing an identity crisis," <i>Science</i> 274: 1664-1672;	
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	15	FAY, D.S. et al. (1997) "Mutations in SPK1/RAD53 that specifically abolish checkpoint but not growth-related functions," <i>Curr. Genet.</i> 31: 97-105;	

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	Examiner Name	K. Canella
Attorney Docket No.		0575/56615-A-PCT-US/JPW/AJM/MVM

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	16	JAMES, P. et al. (1996) "Genomic libraries and a host strain designed for highly efficient two-hybrid selection in yeast," <i>Genetics</i> 144: 1425-1436;	
	17	KATO, R. et al. (1994) "An essential gene, <i>ESR1</i> , is required for mitotic cell growth, DNA repair and meiotic recombination in <i>Saccharomyces cerevisiae</i> ," <i>Nucleic Acids Res.</i> 22: 3104-3112;	
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	27	VALLEN, E.A. et al. (1999) "Interaction between the MEC1-dependent DNA synthesis checkpoint and G1 cyclin function in <i>Saccharomyces cerevisiae</i> ," <i>Genetics</i> 151: 459-71;	
	28	WANG, Y.A. et al. (1997) "Loss of p21 increases sensitivity to ionizing radiation and delays the onset of lymphoma in atm-deficient mice," <i>Proc. Natl. Acad. Sci. USA</i> 94: 14590-14595;	
	29	WESTPHAL, C.H. et al. (1997) "Genetic interactions between atm and p53 influence cellular proliferation and irradiation-induced cell cycle checkpoints," <i>Cancer Res.</i> 57: 1664-1667;	
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	32	ZAKIAN, V.A. (1995) "ATM-related genes: what do they tell us about functions of the human gene?," <i>Cell</i> 82: 685-687;	
	33	ZHENG, P. et al. (1993) "SPK1 is an essential S-phase-specific gene of <i>Saccharomyces cerevisiae</i> that encodes a nuclear serine/threonine/tyrosine kinase," <i>Mol. Cell. Biol.</i> 13: 5829-5842;	
	34	BARRELL et al. (1997) (Genbank Accession No. Z46729, National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland);	
	35	LEWIN (1988) "When Does Homology Mean Something Else?" <i>Science</i> 237: 1570;	
	36	MIYAKAWA et al. (1991) Genbank Accession No. X54964 (National Center for Biotechnology Information, National Library of Medicine; Bethesda, Maryland);	
	37	REECK et al. (1987) "Homology In Proteins and Nucleic Acids: A Terminology Muddle and a Way Out of It," <i>Cell</i> 50: 667;	
	38	SAMBROOK et al. (1987) <i>Molecular Cloning, a Laboratory Manual</i> (Cold Spring Harbor Press): 16.3-16.4;	
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Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Application Number	09/814,661
	Filing Date	March 22, 2001
	First Named Inventor	Rodney Rothstein
	Art Unit	1642
	Examiner Name	K. Canella
Attorney Docket No.		0575/56615-A-PCT-US/JPW/AJM/MVM

NON PATENT LITERATURE DOCUMENTS

Examiner Initials [*]	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	40	AHN et al. (1993) "The Structural and Functional Diversity of Dystrophin," <i>Nature Genetics</i> 3: 283-291;	
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	46	BRADFORD, M.M. (1976) "A Rapid and Sensitive Method For The Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding," <i>Anal. Biochem.</i> 72: 248-254;	
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